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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/748,010	NOELLE ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-61,64,65,67-76,79,80,82-88,91-97,99-105 and 107* is/are rejected.

7)☒ Claim(s) *62,63,66,77,78,81,89,90,98,106* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Previously pending claims have been canceled in favor of new claims. As a result, previous rejections are moot.

Claim Objections

Claims 58, 61, 65, 73. 80, 85 and 106 are objected to because of the following informalities: Claim 58, line 6, "mounts" should be --amounts--. Claim 61, line 2, "(CD40L) L" should be --(CD40L)--. Claim 65, line 2, there are 2 commas after "polyIC". Claim 70 has two perids. Claim 73, line 6, --(iv)-- is missing after "and". Claim 80, line 2, there are 2 commas after "polyIC", and there are 2 periods at the end of the sentence. Claim 85, there are 2 periods at the end of the sentence. Claim 89, there are 2 periods after the claim number "89". Claim 106, line 2, there is a period after the first occurrence of "antibody". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58, 65, 80 and dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 58 is indefinite because in line 6, it recites "wherein (i) and (ii) are comprised in [a]mounts such that, in combination with the other, are effective...." It is unclear what "the other" is referring to. This rejection could be obviated by rephrasing such as, "wherein (i) and (ii) are each comprised in an [a]mounts such that, in combination with the other, are effective..." (see claim 73 for acceptable language).

Claims 65 and 80 are indefinite because they recite "or any combination of any of the foregoing." This includes a combination of a single compound, which is indefinite. This rejection could be obviated by deleting "of any" from the phrase.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 58-61, 64-65, 67-76, 79, 80, 82-88, 91-97, 99-105 and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krug et al. (Eur. J. Immunol, 31:3026, Oct. 2001) in view of Melief et al. (Immunological Rev., 188:177, Oct. 2002, cited by Examiner 9/15/06), Vonderheide et al. (J. Clin. Oncolo. 19(13):3280-3287, 01 July 2001), and Singh et al. (Pharm. Res., 19(6):715-728, June 2002).

Krug et al. teaches an immunostimulatory combination of CD40 ligand (CD40L) with CpG oligodeoxynucleotide (ODN), which is a TLR9 agonist. The combination synergistically activates plasmacytoid dendritic cells (PDC) (e.g., p. 3027 and p. 3029, first paragraphs of each col. 2). It also induced a large increase in IFN-y-producing T cells (Fig. 9). Krug et al. also teach (p. 3026, last paragraph), "As a vaccine adjuvant, CpG DNA is at least as effective as the gold standard complete Freund's adjuvant (CFA), but has higher Thl activity and lower toxicity .... " They also discuss the importance of"CD40 ligation" in obtaining significant PDC responses (p. 3033, col. 1, third and fourth paragraphs), stating (last two sentences beginning p. 3033): "Our data support the view that PDC in the presence of the appropriate, microbial stimulus and CD40 ligation induce an IL-12-dependent Thl response .... Selective amplification of T cell-derived signals might explain why CpG ODN acts as a potent Thl adjuvant in vivo without causing major

toxicity or autoimmunity." Krug et al. do not teach a vaccine or immunostimulatory composition suitable for human administration comprising an agonist of TLR9 and CD40.

Melief et al. teach therapeutic anticancer vaccines. They also teach that an agonistic monoclonal antibody against CD40 turned a preventative vaccine against human papilloma virus 16 into a therapeutic vaccine in mice and in some cases, administration of an anti-CD40 antibody alone was sufficient to completely eradicate tumors (p. 178, col. 2, 2nd paragraph). Finally (p. 181, top of col. 2),

"It is now possible to design entirely synthetic vaccines that provide both the proper antigenic and accessory signals for induction of full scale CTL [cytolytic T-lymphocyte] effector burst as well as CTL memory. These signals employ molecularly defined innate immunity receptors such as those belonging to the TLR family, and/or adaptive immunity receptors such as CD40 or Fc receptors (Table 1). In cancer, it is precisely the triggering of these receptors that is lacking .... Provision of the proper TLR ligands from the microbial realm will drastically enhance these abortive responses and turn them into strong tumoricidal effector responses capable of eradicating established cancers. Both for preclinical research and for preparation and application of clinical grade vaccines, entirely synthetic formulations offer marked advantages. Rather than rely on poorly defined immune system triggers, such as recombinant vectors and adjutants without molecularly defined function, the novel generation of TLR ligand- mimicking adjuvants induces very precise signal transduction pathways in professional APC [antigen-presenting cell] that, moreover, can be further- manipulated for desired effect by very precise changes in the ligands."

CpG-ODN adjuvant provided immunity against human papilloma virus-induced mouse tumors (p. 181, first full paragraph).

Vonderheide et al teach human phase I clinical trials with CD40 ligand administered to cancer patients. The CD40L was human and made recombinantly. Aside from transient liver transaminase elevation (p. 3286, col. 2, second sentence of last paragraph), CD40L was well tolerated and showed antitumor activity (p. 3285, col. 2, last paragraph). Additionally, an antitumor effect of the ligand related to immune stimulation was observed in the enhancement of antigen presentation by dendritic cells, monocytes, B cells, and the triggering of antigen-specific, T-cell responses. Also, CD40L is being tested in patients with B-cell lymphoma or leukemias (p. 3281, col. 1, second full paragraph). It is stated (p. 3285, col. 2, end of first full paragraph) that "CD40 ligation has been effectively exploited for the induction of antitumor immunity in several animal models."

Singh et al. teach the importance of dendritic cells (DCs) in antigen uptake and its transfer to lymph nodes, allowing for presentation to T cells (paragraph bridging cols. 1-2 on page 716). Table 1 shows that CpG oligos have been evaluated in clinical trials as vaccine adjuvants. It is reported (p. 717, paragraph 1 of col. 2) that, "The Th1 adjuvant effect on CpG. appears to be maximized by their conjugation to protein antigens (40) or their formulation with delivery systems..." Singh et al . discuss routes of administration of immunostimulatory adjuvants, including by intramuscular (i.m.) immunization (Fig. 1), subcutaneous injection and particular and micorparticle antigen delivery which may be i.m. or muscosal, which includes oral and intranasal (col. 2 of page 720-21). It is also states that traditional routes of administration have been i.m. and subcutaneous (p. 720, col. 2).

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have a vaccine comprising the TLR9 agonist, CpG ODN, in combination with a CD40 stimulating agent such as an anti-CD40 agonist antibody or CD40L in order to induce an immune response in a human against an antigen, such as from bacteria. The vaccine would have been obvious and desirable because Krug et al. showed that CpG ODN acted synergistically with CD40L to stimulate a T cell response. Krug et al. also say that CpG ODN is a potent Thl vaccine adjuvant and notes that CD40 ligation is important for the synergism, implying that what is important for synergism is the CD40 activation instead of what activates CD40. Melief et al. showed the use of a CD40 agonist antibody enhanced activity of a viral vaccine. The CD40 agonist antibody necessarily ligated CD40. Melief et al. also said that synthetic TLR ligands are very useful in vaccines, allowing for induction of "very precise signal transduction pathways", and in combination with a CD40 agonist should provide a means for destroying established cancers. Similarly, Vonderheide et al. showed that CD40L produced an immunostimulatory antitumor effect when administered to human cancer patients and that the toxicity was transient and the compound relatively well tolerated. They additionally disclosed that CD40L has shown antitumor activity in several animal model. Singh et al. disclosed the use of CpG oligos in clinical trials as adjuvants for vaccines. Previously tested administration routes for immunostimulatory adjuvants, such as i.m., subcutaneous and mucosal, were also discussed. A specific example was provided for CpG ODN, which may function as a tumor antigen, viral antigen and bacterial antigen according to Krug et al. and Melief et al. One would have

reasonably expected synergy *in vivo* from the composition comprising CpG ODN and a CD40 agonist because of the teachings of Krug et al., which supports the interaction of the two compounds whether *in vitro* or *in vivo* and whether CpG ODN is being expressed by a cell or included in a composition. For these reasons the invention is obvious.

Applicants' arguments which pertain to the new rejection above made in response to the amendment to the claims are addressed here.

Applicants argue (pages 18-19) that Krug et al. taken alone or in combination with Melief et al. does not teach or suggest the claimed immunostimulatory compositions or vaccines because Krug et al. has only *in vitro* studies directed at understanding the effects of CpG as an adjuvant on cells. The argument has been fully considered, but is not persuasive. Melief et al. teach vaccines, including the desirability of including CpG in a therapeutic vaccine, and that CpG-ODN adjuvant provided immunity against human papillomavirus-induced mouse tumors (p. 181, first full paragraph). Similarly, an agonistic CD40 antibody turned a preventative vaccine against human papilloma virus 16 into a therapeutic vaccine in mice (p. 178, col. 2, 2nd paragraph). Also, they state, "Rather than rely on poorly defined immune system triggers, such as recombinant vectors and adjutants without molecularly defined function, the novel generation of TLR ligand- mimicking adjuvants induces very precise signal transduction pathways in professional APC [antigen-presenting cell] that, moreover, can be further- manipulated for desired effect by very precise changes in the ligands." These showings combined with the those of Krug et al. that CD40L and CpG can act synergistically to stimulate immune cells provides not only motivation to have a vaccine which combines a CD40 agonist and CpG, but also a reasonably expectation of a synergistic interaction of both compounds in the composition, particularly taken in view of the teaches of Singh et al. and Vonderheide et al. discussed above that show the therapeutic advantage of using CpG and a CD40 ligand, respectively.

Applicants argue (paragraph bridging pages 19-20) that because the authors of Krug et al., which includes Arthur Krieg, do not reference any of the many patents of Krieg disclosing the combination of CD40 agonist and TLR agonist, the combination is not obvious. That is, no Krieg patent or application discloses the desirability of combining CD40 agonist with CpG, supporting the assertion that the skilled artisan would not have thought to co-administer CpG and

CD40L. The argument has been fully considered, but is not persuasive. As can be clearly seen from the references cited above, Krug et al. teach synergism of CD40L and CpG in activation of immune cells and Melief et al. state, "These signals employ molecularly defined innate immunity receptors such as those belonging to the TLR family, and/or adaptive immunity receptors such as CD40 or Fc receptors (Table 1). In cancer, it is precisely the triggering of these receptors that is lacking .... Provision of the proper TLR ligands from the microbial realm will drastically enhance these abortive responses and turn them into strong tumoricidal effector responses capable of eradicating established cancers." It is irrelevant if the article by Krug et al. cites patents or applications. It is extremely rare, if ever, that non-patent literature cites patents or application.

Applicants argue that Ahonen et al., J. Exp. Med., 2004, by the inventors "is widely cited by scientific peers of the inventors as being the first evidence as to the synergistic effect of TLR/CD40 agonists in vivo. As evidence for this fact a listing of references citing the Ahonen article is attached to this Amendment Reply as Appendix B." The argument has been fully considered, but is not persuasive. The examiner does not have the resources to review each of the 26 references listed. The references were not made of record on an IDS. The examiner did briefly read several of the reference for basis of Applicants' argument. Habib et al. (J. Immunol, 2007) does not list Ahonen as an exclusive reference to synergy. Rus et al. (J. Immunol., 2007), refers only to Ahonen for an assay methodology. Kochenderfer et al., (J. Immunol., 2006) refers to Ahonen not for a showing of synergy but for IFN-dependence. None of the 3/3 references the Examiner looked at support Applicants' claim of the inventors being the first to recognize the synergistic effect of TLR/CD40 agonists *in vivo*.

Applicants argue (pages 20-21) that Krug et al. has only *in vitro* studies using plasmacytoid dendritic cells (PDCs), which is not and was not at the time the invention was made thought to play a role in adaptive antigen specific immunity. Applicants cite two Fonteneua et al. references (2003 and 2004, which have been made of record by the Examiner in the attached PTO-892) that suggest myeloid dendritic cells instead play a more significant role in adaptive antigen specific T cell immunity. The argument has been fully considered, but is not persuasive. First, it was appropriate for Krug et al. to have used PDCs as supported by Sabroe et al. (Clin. Exp. Allergy, 32:984, 2002), who state (p. 985, middle of col. 1), "Within the dendritic cell (DC) subset, CpG responses appear confined to dendritic cells of plasmacytoid lineage,

rather than myeloid-derived DC [40, 41]. This is in keeping with TLR expression patterns, since myeloid DCs express TLRs involved in LPS responses while plasmacytoid DCs do not express TLR2 or TLR4, do not respond to LPS and peptidoglycan, but do express TLR9 [38, 40, 41]." Also (p. 987, first paragraph), "The cellular response to bacterial CpG includes B cell proliferation and immunoglobulin secretion [42], dendritic cell maturation [38, 40, 41] and enhanced APC function...." The Fonteneau et al. references do not refute but, instead, support the role of PDCs in immune response. In the abstract of Fonteneau et al. J., Virol. 78(10):5223-32, May 2004 (supplied by Applicants in the Appendices of the reply filed 7/20/07 on page 109), it says:

> pDCs exposed to different strains of infectious or even chemically inactivated, nonreplicating HIV-1 strongly upregulated the expression of maturation markers, such as CD83 and functional CCR7, analogous to exposure to R-848, a synthetic agonist of toll-like receptor-7 and -8. In addition, HIV-l-activated pDCs produced cytokines (IFN-alpha and tumor necrosis factor alpha), migrated in response to CCL19 and, in coculture, matured [myeloid] CD11c+ DCs, which are not directly activated by HIV. pDCs also acquired the ability to stimulate naive CD4+ T cells, albeit less efficiently than CD11c+ DCs.

In the abstract of Fontenau et al., Blood, 101(9) :3520-6, May 2003 (supplied by Applicants in the Appendices of the reply filed 7/20/07 on page 110), it says:

> pDCs were compared with [myeloid] CD11c(+) DCs, the most potent antigen-presenting cells (APCs), for their capacity to activate T-cell responses. We found that like CD11c(+) DCs, pDCs mature following exposure to influenza virus, express CCR7, and produce proinflammatory chemokines, but differ in that they produce type I IFN and are resistant to the cytopathic effect of the infection. After influenza virus exposure, both DC types exhibited an equivalent efficiency to expand anti-influenza virus cytotoxic T lymphocytes (CTLs) and T helper 1 (TH1) CD4(+) T cells. Our results pinpoint a new role of pDCs in the induction of antiviral T-cell responses and suggest that these DCs play a prominent role in the adaptive immune response against viruses.

Therefore, the art support supports the use of PDCs in the study of immune response.

Applicants argue that the article of Sanchez et al. (J. Immunol. 178:1564-1572, 2007), which includes one of the instant inventors shows that *in vivo* the synergy between TRL9 and CD40 agonist is CD70 dependent, and PDCs don't express CD70. The argument has been fully considered, but is not persuasive. First, cell culture is widely recognized as a reasonable model

for *in vivo* cell activity. Second, even though Sanchez et al. showed that PDCs did not response to CD40 agonist and a TLR 1/2 agonist either alone or together (Fig. 3B), this is not on point for the rejection above which relied on a CD40 agonist and TLR9 agonist. The art clearly shows that not all dendritic cells express all TLRs. Sabro et al. (*Ibid)* clearly state (see the preceding paragraph) that, "plasmacytoid DCs do not express TLR2". If there is no receptor for the TLR agonist to activate, it is of no surprise if a response is absent. Further, Fonteneau et al., J. Virol., 2004, cited above say that PDCs activated by HIV-1 cause the maturation of myeloid CD11c+ DCs. The *in vivo* activity of PDCs may be to affect other types of DCs. The reference of Sanchez et al. in no way takes away from the validity of the results of Krug et al.

Applicants argue (bottom of p. 21) that the toxic effects a of TLR agonist and CD40 agonist would have disfavored the combination in immunotherapy. The argument has been fully considered, but is not persuasive. As can be seen by Vonderheide et al. who discussed human phase I clinical trials with CD40 ligand and Singh et al. who showed that CpG oligos have been evaluated in clinical trials as vaccine adjuvants, toxicity appears to be primarily transient and not a hindrance to use of either compound alone or, one would reasonably expect, together. Even though Applicants' Appendix C shows "in vitro toxicity data obtained by the inventors relating to TLR./CD40 agonist combination" which produced lower liver toxicity than CD40 agonist alone, as discussed above in reference to Vonderheide et al., the CD40 liver toxicity is transient. This is supported by Applicants' own data in Appendix C. Therefore, even if the short-term toxicity is less, the eventual outcome at about 75 hours is the same. It is noted that experiments in Appendix C are not represented for **TLR9 CpG**/CD40 agonist combination,

As to the text on pages 1-3 of Appendix C, it is unclear if this is from an article. It is clearly not a declaration. It is not signed by the attorney or inventor. The text section is not specifically referred to in Applicants' arguments. Therefore, it has not been considered.

Applicants argue (p. 22) that the present invention achieved two unexpected results: 1) synergy between a TLR and CD40 agonist in immune response, and 2) reduction in liver toxicity when the two types of agonists are combined. The argument has been fully considered, but is not persuasive. As discussed in length above, the synergy between TLR9 agonist CpG and a CD40 agonist is not unexpected in view of the prior art. Further, the claims do not have a limitation directed to reduction of liver toxicity when the two types of agonists are combined, nor

does the art support a reason to suspect that liver toxicity would prevent the *in vivo* use of either agonist alone or together since both have been tested in human clinical trials and found to be without serious toxicity effects that would prevent their further use.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gantner et al. (Eur. J. Immunol., 33 :1576-85, June 2003) was published before the filing date of the instant application but after the filing date of the provisional application to which this application claims benefit of priority, so it is not available as prior art. It is, however, being made of record as being published prior to Ahonen et al. (J. Exp. Med., 199(6), Mar. 2004), which applicants refer to in their response as discussed above. Gantner et al. report (p. 1578, end of col. 2), "The addition of CpG-ODN to [human] tonsil B cell-CHO/CD40L co-cultures synergistically increased B cell proliferation in a concentration-dependent manner...."

Conclusion

Claims 62,63,66,77,78,81,89,90,98 and 106 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.
Patent Examiner, Art Unit 1646
September 28, 2007

LORRAINE SPECTOR
PRIMARY EXAMINER